REMARKS

Prior to entry of the amendments presented above, claims 1-32 were pending in the application. Claims 1-10 and 24 have been canceled, claims 11, 13-15, 19-20, 29 and 31 have been amended and claim 33 has been added. The cancellation of claims is made herein without prejudice or disclaimer of the subject matter recited therein, and applicants expressly reserve all rights to such subject matter, including the right to file continuation and/or divisional applications. The amendments are fully supported by the specification. Claims 11-23 and 25-33, including independent claim 11, are thus pending for reexamination and reconsideration, which are respectfully requested in view of the foregoing amendments and following remarks.

In the Office Action, claims 1-27, 29 and 31-32 were rejected under 35 USC § 112, second paragraph, as indefinite. Claims 1-7, 9-10, 19, 24, 29 and 31-32 were rejected under 35 USC § 102(b) as anticipated by Kool. Claims 1-7, 9-12, 16-19, 29 were rejected under 35 USC § 102(e) as anticipated by Tuschl. Claims 1-3, 7-12, 16-17, 19 21-25 and 31-32 were rejected under 35 USC § 102(e) as anticipated by McSwiggen. Claims 1-10, 19-20, 24, 29, and 31-32 were rejected under 35 USC § 103(a) as obvious Kool in view of Beigelman and Holen. Claims 1-3, 7-8, 10-14, 16-17, 19, 21-27, 29 and 31-32 were rejected under 35 USC § 103(a) as obvious over McSwiggen in view of Crooke and Kool. The specific grounds of rejection, and applicants' response thereto, are set forth in detail below.

Support for the amendments

The amendments to claim 11 are supported throughout the specification, in the language of original claim 11, and in the drawings, for example Figures 2, 10, 11, 15 and 16. Claim 22 is supported at page 4, lines 8-10 of the specification.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-27, 29 and 31-32 are rejected under 35 USC § 112, second paragraph, as indefinite. Specifically, the Examiner states that a "ribonucleic acid is simply A, C, G or U and, therefore, cannot comprise a double-stranded structure." The Examiner also objects to certain recitations in claims 13-15 for lack of antecedent basis. Applicants respectfully traverse.

With respect to the nature of ribonucleic acid, applicants respectfully submit that the Examiner is incorrect and that the claim language is fully consistent with the usage in the art, and that the skilled artisan is fully apprised of the scope of the claimed invention. A ribonucleic acid is not simply A, C, G or U but is a polymer made up of monomers such as A, C, G and U which are linked to each other by their phosphodiester groups. The skilled artisan will understand that a ribonucleic acid can be single-stranded, double-stranded or sometimes even triple-stranded, and therefore the claim recitation that the ribonucleic acid molecules be double stranded merely specifies one of these possible structures. Indeed, later in the office action the Examiner states that Kool teaches a "ribonucleic acid double stranded structure." This statement is incompatible with the instant rejection. If the Examiner maintains this rejection applicants respectfully request that the Examiner provide evidence that one skilled in the art would understand ribonucleic acid to be "simply A, C, G or U." Applicants respectfully submit that the claims are fully compliant with the second paragraph of § 112 and, accordingly, request withdrawal of the rejection.

With respect to the rejections of claims 13-15 applicants respectfully submit that the claim amendments presented above render the rejections moot.

Rejections under 35 U.S.C. § 102

Claims 1-7, 9-10, 19, 24, 29 and 31-32 are rejected under 35 USC § 102(b) as anticipated by Kool. Claims 1-7, 9-12, 16-19, 29 are rejected under 35 USC § 102(e) as anticipated by Tuschl. Claims 1-3, 7-12, 16-17, 19 21-25 and 31-32 are rejected under 35 USC § 102(e) as anticipated by McSwiggen. Applicants respectfully traverse, and address the rejections in the order set forth in the office action.

It is axiomatic that, for a prior art reference to be anticipatory, every element of the claimed invention must be identically shown in a single reference. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990). For the reasons set forth below, none of the cited references describes every element of the claimed invention and, accordingly, cannot anticipate or render obvious the claimed invention.

Kool

This rejection is moot in light of the claim amendments presented above.

Tuschl

The Examiner alleges that Tuschl discloses a double-stranded structure having a plurality of groups of modified nucleotides modified at the 2' position, flanked by modified or unmodified nucleotides that consist of 1 to 10 nucleotides. In particular, the Examiner cites paragraph 0016 and figure 14 of Tuschl as disclosing this structure. However paragraph 0016 of Tuschl merely describes the chemical nature of certain nucleotide analogues and the corresponding modifications that can be made in Tuschl's siRNA molecules, and is silent regarding whether there is actually a plurality of groups of such modified nucleotides.

Indeed, paragraph 0015 of Tuschl seems to be more relevant to the instantly claimed invention. Paragraph 0015 discloses that the RNA molecule may contain at least one modified nucleotide analogue (as further defined in paragraph 0016). However, neither paragraph states that both the sense and antisense strand of the RNA molecule exhibits such modified nucleotide analogue, nor is there any disclosure regarding any pattern of a plurality of groups of modified nucleotides. Rather, paragraph 0015 states that such analogues should located at positions where the target-specific activity is not substantially affected, *i.e.* in a region at the 5' end and/or the 3' end of the double-stranded RNA molecule, which purportedly allow the overhangs to be stabilized.

Fig. 14 of Tuschl (and as explained in more detail in Tuschl paragraph 0140) merely discloses an overhang of modified ribonucleotides at the 3' end of both strands of the RNA molecule. However, a group of 2' deoxy or 2'-O-methyl modified nucleotides at the termini of both the antisense strand and the sense strand does not provide a pattern of a plurality of groups of modified nucleotides as recited in instant claim 11.

Accordingly, Tuschl does not describe a double stranded RNA molecule having a plurality of groups of modified nucleotides on each strand of the molecule and therefore does not teach each and every element of the claimed invention. Accordingly, applicants respectfully request withdrawal of the rejection.

McSwiggen

The Examiner asserts that McSwiggen discloses a double-stranded structure comprising a plurality of groups of modified nucleotides modified at the 2' position, flanked by modified or unmodified nucleotides that consist of 1 to 10 nucleotides. The Examiner specifically refers to Fig. 5 of McSwiggen for this purported teaching. However, later in the office action the Examiner admits that "McSwiggen et al. does **not** teach a double-stranded structure with a pattern of modified nucleotides." (see paragraph bridging pages 10 and 11 of the office action, emphasis added). Moreover, McSwiggen's description of modified nucleotides, as set forth in paragraphs 0020 and 0021, specifies that only the *pyrimidine nucleotides* are modified as 2'-O-methyl or as 2'-deoxy-2'-fluoro pyrimidines. Accordingly, this modification is defined by the presence or absence of pyrimidine nucleotides (*i.e.* by the nucleic acid sequence) and therefore cannot contain any pattern, *i.e.* a *regular* arrangement or sequence of modified and unmodified nucleotides as recited in instant claim 11. This is also confirmed by Fig. 5 of McSwiggen where no pattern, *i.e.* regular arrangement or sequence of modified and unmodified nucleotides is disclosed.

Accordingly, McSwiggen does not describe a double stranded RNA molecule having a pattern of modified nucleotides on each strand of the molecule and therefore does not teach each and every element of the instantly claimed invention. Accordingly, applicants respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 103(a)

Claims 1-10, 19-20, 24, 29, and 31-32 are rejected under 35 USC § 103(a) as obvious over Kool in view of Beigelman and Holen. Claims 1-3, 7-8, 10-14, 16-17, 19, 21-27, 29 and 31-32 are rejected under 35 USC § 103(a) as obvious over McSwiggen in view of Crooke and Kool. Applicants respectfully traverse, and address the rejections in the order set forth in the office action.

Kool in view of Beigelman and Holen

This rejection is moot in light of the claim amendments presented above.

McSwiggen in view of Crooke and Kool

The Examiner admits that McSwiggen does not teach or suggest a double stranded structure with a pattern of modified nucleotides but asserts that Crooke remedies this defect by teaching a ribonucleic molecule having a pattern of modified and unmodified nucleotides. The Examine also admits that neither McSwiggen nor Crooke teach or suggest a loop structure comprising a non-nucleic acid polymer, but asserts that this deficiency is remedied by Kool. Applicants respectfully traverse.

When combining references to make out a *prima facie* case of obviousness, the examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion/motivation to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (holding that is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* MPEP §§ 2142-43 (August 2001). In the present case, the Examiner has failed to set forth adequate reasons as to why one of ordinary skill in the art would have been motivated to combine the cited references, nor has the Examiner set forth a reason why one of ordinary skill in the art would have had a reasonable expectation of success. Accordingly, no *prima facie* case of obviousness exists, and the rejection should be withdrawn.

As an initial matter, although McSwiggen deals with siRNA molecules, the disclosure of Crooke is related to *antisense* oligoribonucleotides, and not siRNA molecules. Antisense molecules act through the formation of a duplex with mRNA and activation of RNAseH, a double-strand specific nuclease. By contrast, the various enzymes involved in the siRNA-mediated RNA interference mechanism are quite different and include, among others, the so-called dicer complex. In light of these major differences, there would have been no motivation for one of ordinary skill in the art to combine the teachings of Crooke , which apply exclusively to antisense molecules, with those of McSwiggen, which apply to siRNA molecules.

The Examiner asserts that Crooke teaches a ribonucleic acid having modified nucleotides which are flanked by unmodified nucleotides. However, Crooke's only specific disclosure in this

regard is contained in figure 1 and at column 13, lines 21 to 45. Neither of these descriptions teach or suggest a pattern of modified nucleotides as recited in the instant claims.

Moreover, Crooke is directed only to single stranded antisense molecules and is silent regarding the design of a respective complementary strand. This is not surprising given that antisense oligonucleotide technology makes use of single-stranded oligonucleotides that bind to naturally occurring mRNA to form a double-stranded structure molecule. The resulting double stranded structure would, by definition, contain an unmodified RNA strand (the mRNA target), in contrast to the present invention in which both strands contain a pattern of modified nucleotides. Nothing in Crooke teaches or suggests a double stranded RNA molecules in which patterns of modified nucleotides occur in both strands of the RNA.

The Examiner states that one skilled in the art would have been "motivated to make a double-stranded structure with modified and unmodified ribonucleic acids in such a pattern because such a pattern increases the affinity of the oligoribonucleic acid compound to the target." Applicants respectfully submit that, if this motivation were correct, then one skilled in the art would have been prompted to make a fully modified ribonucleic acid molecule (so as to have maximum affinity) rather than a pattern of modified and unmodified nucleotides. However, a fully modified siRNA molecule would be completely inactive, as McSwiggen notes that complete substitution of one or both siRNA strands with 2'-deoxy (2'-H) or 2'-O-methyl nucleotides abolishes RNAi activity. See paragraph 5 of McSwiggen. Moreover, the reason Crooke's antisense molecules do not contain fully modified nucleotides is because the antisense molecules require a stretch of deoxy (and therefore unmodified) nucleotides to induce RNase H activity. Nothing in the prior art, however, teaches or suggests that any stretch of deoxy nucleotides is remotely relevant for activating the enzymes involved in RNA interference. In addition, McSwiggen also states repeatedly that any substituted nucleotides should be at the 5' or 3' terminus of the siRNA. See paragraphs 40-55 of McSwiggen. Such substitutions at one or both termini do not constitute a pattern of modified nucleotides as recited in the instant claims.

Furthermore, in light of the major differences between antisense molecules and molecules that induce RNAi, one of ordinary skill in the art would not have had a reasonable expectation of success by applying single stranded antisense molecules having the "pattern" of modified nucleotides purportedly described by Crooke in the double stranded siRNA molecules described

by McSwiggen. Indeed, as described above, McSwiggen states that complete substitution of one or both siRNA strands with 2'-deoxy (2'-H) or 2'-O-methyl nucleotides abolishes RNAi activity. Accordingly, one skilled in the art would not have had a reasonable expectation that an siRNA molecules containing a pattern of modified nucleotides on both strands would be successful in inducing RNA interference.

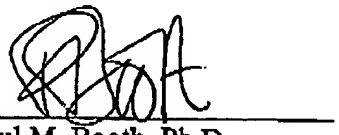
Kool is cited only as teaching a non-nucleic acid linker and fails to remedy the deficiencies of McSwiggen or Crooke.

In sum, for the reasons set forth above, one or ordinary skill in the art would not have been motivated to combine the cited references, and would not have had a reasonable expectation that the combination would be successful. Accordingly, no *prima facie* case of obviousness exists and the rejection should be withdrawn.

CONCLUSION

In view of the above amendment and remarks, applicants respectfully request that all objections and rejections be withdrawn and that a notice of allowance be forthcoming. The Examiner is invited to contact the undersigned attorney for applicants at 202-912-2197 for any reason related to the advancement of this case.

Respectfully submitted,



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